Rhodamine-123 to substantially decrease the level of prostate specific acid phosphatase in the blood of the patient.

27. A method for treating a patient with prostate cancer comprising dissolving Rhodamine-123 in a solvent which includes ethyl alcohol to form a stock solution, diluting the stock with water to form a treatment solution which includes Rhodamine-123, water and ethyl alcohol, administering the treatment solution to the patient in an amount sufficient to effect *in vivo* destruction of prostate cancer cells, measuring the patient's prostate specific acid phosphatase level before and after treatment, and administering sufficient Rhodamine-123 to substantially decrease the level of prostate specific acid phosphatase in the blood of the patient.

IN THE ABSTRACT

Delete the title beginning at page 21, line 3, and replace it with the following:

COMPOSITION AND METHOD FOR TREATING CARCINOMA

(Replace the paragraph beginning at page 21, line 6 with the following new paragraph:)

C12

Carcinoma is treated in a patient by administration of Rhodamine-123 (Rh-123) orally or by intravenous injection of a treatment solution of Rh-123, ethyl alcohol, dextrose, and water in an amount sufficient to effect *in vivo* destruction of cancer cells. The treatment solution is made by mixing a stock solution of Rh-123 in a solution of 95%ethyl alcohol and 5% water (by volume) with a solution of 5% (by weight) dextrose in water. For prostate cancer, treatment is controlled by measuring the level of prostate specific antigen (PSA), or prostate specific acid phosphatase in the blood of the patient.

REMARKS

The specification and claims have been amended to make it clear that the invention is directed to the treatment of carcinoma, which is any malignant tumor of epithelial origin, of which prostate cancer is one example. As originally stated in the parent and present application, Rhodamine-123 is toxic for carcinoma cells. See page 1, line 24.

Claims 1-27 presently stand rejected as "unpatentable over the Arcadi references (1988) [sic] and (1990) of record for the reason fully set forth in paper no. 4, page 2". Applicant submits with this amendment a copy of a Declaration executed October 30, 2001 by Lawrence W. Jones, M.D., explaining why the Arcadi references of 1986 and 1990 do not provide one skilled in this art "with a reasonable expectation that said rhodamine-123 would be effective to combat said prostatic cancer in human", as contended in the Office action on page 2. As Dr. Jones' Declaration makes clear, at least as early as 1982 rhodamine-123 has been known to reduce the clonal growth of carcinoma cells *in vitro*. The Arcadi references were published in 1986 and 1990. Even so, as late as 1997 there was still substantial professional skepticism about the efficacy of rhodamine-123 for treating human prostate cancer.

As the Jones Declaration also makes clear, hundreds of drugs tested *in vitro* and in laboratory animals have shown potential as antitumor agents, but subsequently failed in clinical tests, or never reached that stage. Moreover, the heterogeneity of prostate cancer makes extrapolation of laboratory results to therapeutic efficacy unreliable.

Also accompanying this amendment is Applicant's Declaration executed February 13, 1997, and submitted with an Amendment dated February 14, 1997 in parent Application No. 08/516,004, filed August 16, 1995. The Applicant is now deceased. His declaration provides evidence that his two prior publications (the Arcadi 1986 and 1990 references) do not make his claimed invention obvious. His declaration explains that neither the saline suspension described in the 1986 reference, nor the DMSO solution described in the 1990 reference, would be acceptable for treating cancer in a human patient.

The Office action dated 10/23/00 (paper no. 4) states on page 2 "With regard to the PSA levels, this is a known test for prostate cancer. The step of showing a lower level clearly teaches that the prior art anti-prostate cancer agent is working." This statement is apparently made with the misunderstanding that it would be obvious to practice the method set forth in the claims which require measuring PSA level in the blood of a patient before and after treatment to determine the effectiveness of the administered medication. If so, this rejection is based on an unsupported supposition, and should be withdrawn. Those skilled in this art have concluded that "PSA reduction cannot be used as a reliable response criterion to evaluate treatment efficacy in individual patients." See the attached copy of the article entitled "Evaluation of Prostate-Specific Antigen as a Surrogate Marker for Response of Hormone-Refractory Prostate Cancer to Suramin

Therapy" by Sridhara, et al, and published in the *Journal of Clinical Oncology*, Vol. 13, No. 12 (December), 1995: pp 2944-2953, which states on the first page under "Conclusion . . . . PSA reduction cannot be used as a reliable response criterion to evaluate treatment efficacy in individual patients."

As is clear from Dr. Jones' declaration, the drug industry and the medical profession have spent millions of dollars and thousands of research hours seeking an effective therapy for prostate cancer. If Dr. Arcadi's 1986 and 1990 articles had actually created a reasonable expectation that treatment with rhodamine-123 would prolong the life of prostate cancer victims, that compound would have been put to wide use instead of being dismissed as clinically inadequate by other workers in that field.

In view of the above evidence and explanation, this application is now in condition for allowance, and such action at an early date is requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

Respectfully submitted,

CHRISTIE, PARKER & HALE, LLP

By R. W. Johnston

R. William Johnston
Reg. No. 17,968
626/795-9900

Enclosures: Declaration of Lawrence W. Jones, M.D.
Applicant's Declaration executed February 13, 1997
Amendment dated February 14, 1997
Article by Sridhara, et al.

RWJ/mc

VERSION TO SHOW CHANGES MADE

TITLE

Delete the title beginning at page 1, line 3, and replace it with the following:

COMPOSITION AND METHOD FOR TREATING ~~[PROSTATE CANCER]~~ CARCINOMA

IN THE SPECIFICATION

Replace the paragraph beginning at page 1, line 10 with the following new paragraph:

This invention relates to compositions and methods for treating ~~[prostate cancer]~~ carcinoma, i.e., a malignant tumor of epithelial origin, with Rhodamine-123 (methyl o-(6-amino-3-imino-3H-xanthen-9-yl) benzoate monohydrochloride).

Replace the paragraph beginning at page 1, line 14 with the following new paragraph:

Metastatic hormone refractory prostate cancer, ~~[which]~~ one of many carcinomas, such as cancer of the breast, liver, pancreas, bladder, lung, skin, colon, and the like, responds poorly to chemotherapy because of its slow rate of replication~~[,]~~. It accounts for about 40,000 deaths annually. There has been no satisfactory treatment for metastatic, hormone refractory prostate cancer. Patients with the disease die with diffuse pain, obstructive renal failure, and bone marrow failure due to replacement by the tumor. Treatment of ~~[this disease]~~ carcinoma needs an agent which is effective independently of the rate of cell division or the ability to interfere with DNA or RNA metabolism.

Replace the paragraph beginning at page 2, line 4 with the following new paragraph:

In terms of a process, my invention provides a method for treating a patient with ~~[prostate cancer]~~ carcinoma by administration of Rhodamine-123 (Rh-123) in an amount sufficient to effect *in vivo* destruction of ~~[prostate]~~ the cancer cells. Preferably, the Rh-123 is administered intravenously in a solution of ethyl alcohol and water. Preferably, the solution includes dextrose, and each dose of Rh-123 is administered to the patient by infusion with between about 10 and

about 250 ml of the Rh-123 solution over a period between about 15 minutes and about 4 hours. The concentration of Rh-123 in the infused solution can be any convenient amount, but normally is between about 1 and about 20 mg/ml.

Replace the paragraph beginning at page 2, line 15 with the following new paragraph:

Preferably, the patient is treated with intermittent doses of Rh-123, which are gradually increased from about 0.5 mg of Rh-123 per kg of patient weight up to about 30 mg per kg of patient weight, or until toxicity is observed, whichever comes first. In the case of prostate cancer, the treatment is continued until the level of prostate specific antigen (PSA) or prostate specific acid phosphatase in the patient's blood decreases significantly from the level prevailing in the patient just prior to treatment in accordance with this invention.

Replace the paragraph beginning at page 2, line 25 with the following new paragraph:

In terms of composition of matter, the invention provides a solution for treating a patient with ~~[prostate cancer]~~ carcinoma. The solution comprises ethyl alcohol and Rh-123 dissolved in water. Preferably, the solution also includes about 5% by weight of a sugar, such as dextrose or glucose, susceptible to metabolic assimilation.

Replace the paragraph beginning at page 2, line 29 with the following new paragraph:

The invention also provides a stock solution for preparing an administration solution used in treating ~~[prostate cancer]~~ carcinoma. The stock solution comprises Rh-123 dissolved in ethyl alcohol (preferably 95% ethyl alcohol and 5% water). The concentration of the Rh-123 in the stock solution is between about 5 and about 25 mg per ml.

In the Claims

Please amend claims 1, 3, 4, 9, 14, and 20 as follows:

1. (Amended) A method for treating a patient with ~~[autochthonous prostate cancer]~~ carcinoma comprising intravenous administration of a solution of Rhodamine-123 in ethyl alcohol and water in an amount sufficient to effect *in vivo* destruction of prostate cancer cells.

3. (Amended) A method according to claim ~~[1]~~ 2 which includes the step of measuring the patient's PSA level before and after treatment, and administering sufficient Rhodamine-123 to substantially decrease the level of PSA in the blood of the patient.

4. (Amended) A method according to claim 1, 2 or 3 which includes injecting the solution in a volume of about 250 ml.

9. (Amended) A solution for treating a patient with ~~[prostate cancer]~~ carcinoma, the solution comprising ethyl alcohol and an effective amount of Rhodamine-123 dissolved in water.

14. (Amended) A stock solution for preparing an administration solution for treating ~~[prostate cancer]~~ carcinoma, the stock solution comprising Rhodamine-123 dissolved in ethyl alcohol.

20. (Amended) A method for treating a patient with ~~[prostate cancer]~~ carcinoma comprising dissolving Rhodamine-123 in a solvent which includes ethyl alcohol to form a stock solution, diluting the stock with water to form a treatment solution which includes Rhodamine-123, water and ethyl alcohol, and administering the treatment solution to the patient in an amount sufficient to effect in vivo destruction of ~~[prostate cancer]~~ carcinoma cells.

IN THE ABSTRACT

Delete the title beginning at page 21, line 3, and replace it with the following:

COMPOSITION AND METHOD FOR TREATING ~~[PROSTATE CANCER]~~ CARCINOMA

Replace the paragraph beginning at page 21, line 6 with the following new paragraph:

~~[Prostate cancer]~~ Carcinoma is treated in a patient by administration of Rhodamine-123 (Rh-123) orally or by intravenous injection of a treatment solution of Rh-123, ethyl alcohol, dextrose, and water in an amount sufficient to effect *in vivo* destruction of [~~prostate~~] cancer cells. The treatment solution is made by mixing a stock solution of Rh-123 in a solution of 95%ethyl alcohol and 5% water (by volume) with a solution of 5% (by weight) dextrose in water. ~~[Treatment]~~ For prostate cancer, treatment is controlled by measuring the level of prostate specific antigen (PSA), or prostate specific acid phosphatase in the blood of the patient.